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Scale of Influence of Substitution in Organic Electrolytes

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SCALE OF INFLUENCE OF SUBSTITUTION IN ORGANIC ELECTROLYTES

BY

RAY WASHINGTON HESS

B. A. Morningside College,
1912

THESIS

Submitted in Partial Fulfillment of the Requirements for the

Degree of

MASTER OF ARTS

IN CHEMISTRY

IN

THE GRADUATE SCHOOL

OF THE

UNIVERSITY OF ILLINOIS

1914

1914
H46

UNIVERSITY OF ILLINOIS

THE GRADUATE SCHOOL

June 1914.

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Ray Washington Hess

ENTITLED Scale of Influence of Substitution

In Organic Electrolytes.

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Master of Arts

C. G. Derick
In Charge of Major Work

W. A. Noyes
Head of Department

Recommendation concurred in:

Committee
on
Final Examination

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Note:-

This table of contents does not imply that all of these substances have been isolated,purified,and characterized,but is merely meant to serve as a brief outline of this investigation.

* INTRODUCTION *

Positive advance in chemistry has always been marked by the quantitative methods of physico-chemical investigation. In following the natural order of progress in its various stages organic chemistry has developed from the qualitative to the quantitative stages. It was physical-chemical methods that finally settled the question of composition. The problem of constitution is still one of much speculation and investigation. Although certain relations between physical properties and constitution have long been known they are limited in their application and lack sufficient generality.

The present day is marked by an increasing tendency to apply the principles of physical chemistry to the solution of the problems of organic chemistry, especially those of constitution and the kinetics of chemical reactions. The exactness of these methods serves a two-fold purpose, that of obtaining more accurate data for the properties of substances already known as well as working out fundamental relationships.

Historical.

It was van't Hoff[1] who first stated that any two atoms in a molecule influence each other in two ways, through intermediate atoms(indirectly) and through space(directly).[2]

A relation between halogen substituted monobasic paraffin acids and their ionization was first recognized and formulated by Ostwald.[3] He established the relation,

$\frac{K_n}{K_o}$ - Place factor.

This ratio of the ionization constant of the substituted acid to that for the unsubstituted acid he calls a " place factor," a quantity depending on the nature and position of the substituent. Using this factor Lichty[4] and Wegscheider[5] have attempted to show the influence of halogens in the normal fatty acids upon ionization.

Flursheim[6] has also studied this effect and greatly confuses the problem by attributing it to polarity of the substituent, the affinity required by it and stearic hindrance.

Adopting the views of van't Hoff and by making use of the Ostwald factor law and many known chemical reactions, Michael has maintained a "scale of combined influence."[7] In a reply[8] to Derick's criticism[9] Michael repeats, "If we number a certain atom in any fatty compound with a normal chain with the figure (1) our present knowledge of the combined mutual influence between this atom and others in the molecule is expressed by the following 'scale of combined influence' the number indicating the degree of removal and the extent of the influence decreasing in the order given 2-3-5-6-4-7-(9-10-11)-8. It is to be strongly emphasised that the effect of any atom in the position (2) or (3) is far greater than that of any similar atom less closely connected, and in the case of atoms further removed the influence must be largely direct i.e. spatial" Assuming that this last statement is true it is quite possible to appreciate his argument for a chain which is composed of carbon atoms only by visualizing the

van't Hoff LeBell conception[10] of the carbon atom with its four valencies radiating to the vertices of a tetrahedron. As shown diagramatically in figure 1 we would have approximately by resolution a pentagonal spiral with the numbers representing carbon atoms. A substituent on any carbon would take the number of the succeeding carbon.

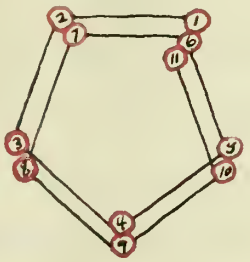


Fig I.

From this it is evident that the influence of an atom at (2) or (3) on another at (1) would be marked, since that of (2) would be entirely spatial whilethat of (3) would be through only one intermediate atom as well as spatial. If we assume that the influence of atoms further removed is mainly spatial then a glance at Fig. 1 will make it clear why Michael places (5) and (6) before (4) in his scale. For the same reason the rest of the scale might be so arranged though it is rather difficult to see the reason for placing (9) ahead of (8) as the distance between (1) and (8) i.e. the direct or space influence, is the same as (1)-(9) and (8) is even one atom in the chain nearer to (1). This space relationship assumes that the force of the valencies may be resolved into the planes of regular pentagons. If this is not done we know but very little about the space relationships existing. This would mean that the valencies of the carbon atom terminates in the vertices of a regular

tetrahedron. There is no phenomena of sterochemistry that justifies such an assumption.[11]

Thus it is seen that there is but little difficulty interpreting Michael's scale for the carbon chain. But we have no method of testing it out in this relation. The difficulty arises when the attempt is made to apply it to organic acids where the influence of one atom upon another may be measured in terms of energy units. In this case the carboxylic hydrogen would be number (1), the hydroxyl oxygen number (2) and the carbon atoms would be numbered as shown in Fig. 11 according to Michael,

Fig II.

A glance at this Fig. is sufficient to make it clear that the relative distances betwee (1) and the other atoms is not at all the same as it was in Fig. I.. One striking point is that (8) which Michael gives the last position in his scale may be as near to (1) as is (3) and should have a space influence nearly as great, which he says is the main influence acting for all positions beyond. In spite of this evident inaccuracy Michael applies his scale to explain the variation in ionization constants of formic, acetic, propionic, butyric, valeric, and caproic acids.[12] Thus he says, "Replacing in formic acid(0.0214) hydrogen by CH_3 brings carbon

4 3 2 1
H-C-O.-H
O

in the relatively unimportant (4) and the three hydrogens in the important (5) position towards the carboxyl hydrogen, which explains the very considerable decrease in the ionization constant in passing from formic to acetic acid(0.0018)"A glance at Fig. 11 will show that while (5) may be a little nearer in space (4) is nearer in the chain so that the influence of these two positions should not be so different. And again, "The change from acetic to propionic acid (0.00134) is much less as in this case a hydrogen in the important position (5) is replaced by the negative carbon, whereby the positive influence of the three hydrogens introduced into the sixth position is neutralized to a considerable extent."The figure shows from a space consideration this should hold fairly well.But he next states, "Butyric acid from propionic acid means the replacement of a hydrogen by a carbon in the important sixth position, while the three introduced hydrogens enter the less important seventh place.This relation is obviously quite different from that in the preceeding examples and it results in an increase of the constant from (0.00134) to (0.00145) that is, one carbon in the important position (6) may exert a greater influence than the three hydrogens in the relatively unimportant position (7)".The inaccuracy of this is very evident as (7) is a little nearer to (1) than is (6).The only way in which (6) could be considered to be nearer to (1) than is (7) is to assume that the angle between the valencies of oxygen is equal to that of carbon.But this is contrary to all accepted views.Even if the consideration was correct here for space relations,Michael has complicated

The problem of introducing other variables, namely positivity negativity, about which nothing quantitative is known. He is dealing with the polarity of carbon and hydrogen without any quantitative measure for it.

Our conclusion then to the consideration of Michael's scale is, that for a chain of carbon atoms we have no means of testing it, and, when applied to organic acids where we may measure the influence of one atom upon another the same space relations do not exist at all so that even from his own argument there is no reason why his scale as so arranged should hold.

* THEORETICAL *

Theoretical.

Realizing that many of the contributions to this field are purely speculative and that the Ostwald factor is not a true measure of the influence of a substituent upon reaction ionization Derick[13], during the last few years has made a comprehensive survey of the field, has clearly defined his terms, and from the second law of thermodynamics has established a fundamental relationship between ionization and structure. He developed it from the well established relation $A = RT \ln K$, where (A) is the free energy of ionization, R is the gas constant, T the absolute temperature and K the ionization constant. As a derivation from this fundamental relation Derick has previously defined the influence of a substituent (I_s) in an organic acid as

$$I_s = \frac{\ln k_o}{\ln k_n} - 1$$

where k_o is the ionization constant of the unsubstituted acid and k_n is the ionization constant of the corresponding substituted acid. The reason he formulated such an expression rather than use the Ostwald factor law was that the second law of thermodynamics shows that the free energy of ionization is a function of the logarithm of the ionization constant and the measure of the influence of an atom must be in terms of a free energy function, since such a function alone is the measure of the tendency of any reaction to occur. Derick then assumes that the free energy of ionization is made up additively of the influence of each atom in the molecule.

In the light of this consideration he holds that the Ostwald factor is not a measure of the influence of a substituent upon ionization as it is not a function of the free energy of ionization and further, that it doed not free the factor from the influence of the other atoms in the molecule but that it is merely a ratio of the ionization constants of the substituted to that of the unsubstituted acids.

Using this expression for (I_s) Derick has worked out the place influence from all the available ionization constants for monobasic paraffin acids. He finds that the influence of a given substituent in a given position is the same regardless of the length of the chain. For example, the α-place influence ($I_{\alpha Cl}$) for acetic acid is (0.6830), that for propionic acid is (0.7083) while that for butyric acid is (0.6826). And further, by applying this to the different positions he finds that the influence of a given substituent in the β-position (I_β) is 1/3 of that for the α-position (I_α) and that of the γ-position (I_γ) is 1/3 of that for the β-position etc, the influence decreasing 1/3 in each succeeding position. Thus for the chlorobutyric acids[13] this relation is made clear.

	Factor.
α-chlorobutyric acid	0.6825
β-chlorobutyric acid	0.1873
γ-chlorobutyric acid	0.0627
δ-chlorovalerianic acid	0.0229

This rule has been applied to the substituents chlorine, bromine, iodine, hydroxyl, and phenyl groups and found to hold.

Reference to Table 1, column 1 will bear this out.

One of the most obvious advantages of this relation for determining structure is that it is necessary to know only the α-influence for a given substitutent. It is clear that the deviation from the rule of thirds could be very large without causing any confusion as to which position the substituent belongs. Ostwald's factor shows no such simple relation as this.

The values in column 1 have been previously calculated by Derick[14] Those in column II have been calculated recently from the same ionization constants.

Table 1.

Name of Acid.	$\frac{\ln k_o}{\ln k_n} - 1$	$\left(\frac{I_s}{2.302\ RT}\right)$
I Chlorine.	(1)	(11)
α-Chloracetic Acid.	0.6830	1.9208
α-Chlorpropionic	0.7083	2.0059
β-Chlorpropionic	0.1901	0.7726
α-Chlorbutyric	0.6826	1.9499
β-Chlorbutyric	0.1873	0.7582
γ-Chlorbutyric	0.0627	0.2840
δ-Chlorvalerianic	0.0230	0.1072
- 11 Bromine.		
-Bromacetic	0.6539	1.8704
α-Brompropionic	0.6312	1.8720
β-Brompropionic	0.2071	0.8299
α-Brombutyric	0.6159	1.8212

Table 1 (con't)

Name of Acid.	$\frac{\ln k_o}{\ln k_n} - 1$	$\frac{I_s}{2.302\ RT}$
11 Bromine.	(1)	(11)
γ-Brombutyric acid	0.0484	0.2118
δ-Bromvalerianic	0.0169	0.0796
111 Iodine.		
- Iodoacetic	0.5138	1.6055
β-Iodopropionic	0.1961	0.7929
γ-Iodobutyric	0.0363	0.1686
δ-Iodovalerianic	0.0061	0.0316
1V Hydroxyl.		
Glycolic Acid	0.2371	0.9066
Lactic Acid	0.2536	0.9785
β-Hydroxypropionic	0.0733	0.3300
γ-Hydroxybutyric	0.0196	0.0924
α-Hydroxy-isobutyric	0.2039	0.8212
γ-Hydroxyvalerianic	0.0214	0.0996
V.Phenyl.		
Phenylacetic	0.1126	0.4787
α-Phenylpropionic	0.1082	0.4721
β-Phenylpropionic	0.0434	0.2004

With the aim of establishing a more exact and simple measure of the influence of a substituent than he has already

obtained from the same fundamental relation A = RT ln k and from the same assumption that the free energy of ionization is made up additively of the influence of each atom in the molecule, Derick[15b] has derived another expression for obtaining a measure of this influence. From the foregoing statement it follows that,

$$I = A = RT \ln k$$

where I is defined as the influence of all the atoms in the molecule upon the free energy of ionization.

For the unsubstituted acid the following relation holds,

$$I_o = A_o = RT_o \ln k_o \qquad (1)$$

where k_o is the ionization constant, T_o the temperature of the solution, A_o the free energy of ionization and I_o the influence of all the atoms in the molecule.

Likewise for the substituted acid we have the expression,

$$I_n = A_n = RT_n \ln k_n \qquad (2)$$

where I_n, A_n, T_n and k_n have values corresponding to those for the unsubstituted acid.

But it is evident that the influence I_n of all the atoms in the molecule of the substituted acid is equal to the influence I_o of all the atoms in a molecule of the unsubstituted acid minus the effect of a single hydrogen atom I_H plus that of the substituent I_s or briefly,

$$I_n = I_o - I_H + I_s \; . \qquad (3)$$

substituting this in equation (2) there results,

$$I_o - I_H + I_s = RT_n \ln k_n \qquad (4)$$

Subtracting equation (1) from equation (4) we have,

$$I_o - I_H + I_s - I_o = RT_n \ln k_n - RT_o \ln k_o$$

which, clearly, reduces to,

$$I_s - I_H = RT(\ln k_n - \ln k_o)$$

if both ionization constants are measured at the same temperature. But Derick has shown that the influence of a single hydrogen atom (I_H) is negligible since its influence is additive to the influence of all the atoms in the molecule[16]. Therefore the influence of a substituent upon the free energy of ionization is given by the equation,

$$I_s = RT(\ln k_n - \ln k_o) \qquad (5)$$

or its equivalent,

$$I_s = 2.302\, RT(\log_{10} k_n - \log_{10} k_o)$$

This expression neglecting the influence of a single hydrogen is the absolute value and is directly proportional to Derick's former measure of this influence,

$$\frac{\ln k_o}{\ln k_n} - 1.$$

Reference to Table 1, by comparing the values in columns I and II makes this obvious. The values in column II represent this newly defined influence, I_s, divided by the constant 2.302 RT. This expression simplifies the calculations and for relative values is just as significant.

That these two different expressions for the measure of

the influence of a substituent are proportional is clearly shown mathematically also. We may equate them by multiplying the old measure of this influence by the constant - 2.302 ln k_n thus,

$$2.302\ RT(\ln k_n - \ln k_o) = -2.302\ RT\ \ln k_n\left(\frac{\ln k_o}{\ln k_n} - 1\right)$$

which, by simplification of the right hand member, reduces to the equality,

$$RT(\ln k_n - \ln k_o) = RT(\ln k_n - \ln k_o)$$

Thus it is seen that the fact that these two values are not numerically equal has no significance, as it is the ratio of the place influences that is the all important consideration in maintaining the rule of thirds.

It is interesting to observe the relation between the Ostwald factor and Derick's place influence as defined in this thesis. The Ostwald factor,

$$\frac{K_n}{K_o} = \text{Factor}$$

may be expressed as,

$$\log K_n - \log K_o = \log \text{Factor}.$$

Solving for the value of $\log K_n$ and substituting in

$$I_s = 2.302\ RT(\log k_n - \log k_o),$$

gives,

$$I_s = 2.302\ RT\ \log \text{Factor},$$

or,

$$\log \text{Factor} = \frac{1}{2.302\ RT} \times I_s$$

This equation shows that the logarithm of the Ostwald Factor is proportional to Derick's place influence.

Object.

The present investigation was undertaken with the hope of contributing something to the quantitative measure of the influence of one atom upon another in the carbon chain. Derick's rule of thirds has been tested out extensively and found to hold approximately for all available data, most of which is quite incorrect. Data for the measurement of the influence of substituents in the δ-position is very meagre while that for the ε-position is not available at present. The desire of placing an atom of oxygen in this ε-position, to synthesize δ-acetyl-valerianic acid, purify it, and obtain its ionization constant for a contribution towards this end is offered in justification of the following.

* SYNTHESIS OF δ-ACETYL VALERIANIC ACID. *

Historical.

The available data for the characterization of δ -acetyl-valerianic acid is incomplete. It seems never to have been prepared in very appreciable quantities in a pure condition. The reasons are some what obvious. The length of the chain together with the characteristics of the keto group make the synthesis difficult and the large number of similar compounds produced in its formation renders its purification perplexing.

W.H.Perkin[17] has obtained it in small amounts, it seems, from the condensation of ethylene bromide with acetoacetic ester and subsequent decompositions. He reported its melting point to be 40- 42°C. The yield is not stated.

O.Wallach obtained it in an impure condition by the oxidation of 1,2,methyl-cyclohexanone[18] with chromic acid. He reports the melting point at about 50°C. He thinks that it may exist in a tautomeric form or hydrated condition. He also produced it in another investigation by the oxidation of tetrahydrophenylacetic acid.[19]

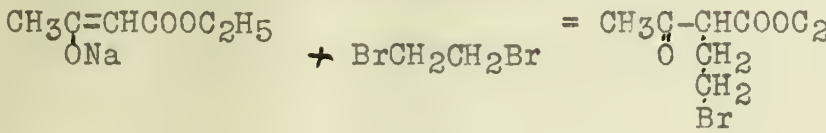
Blaise and Kaeler[20] report a much better yield from the action of a zinc-alkyl-iodide on the half ester of adipic acid chloride. He gives the melting point at 42°C.

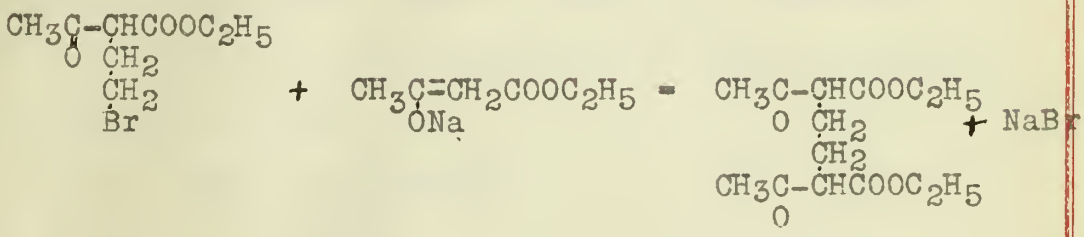
Experimental.

In the attempt to prepare δ -acetyl-valerianic acid five methods were used in this work. It will be impossible to give the large amount of detail here but if desired it may be obtained from the original notes.

Method 1.

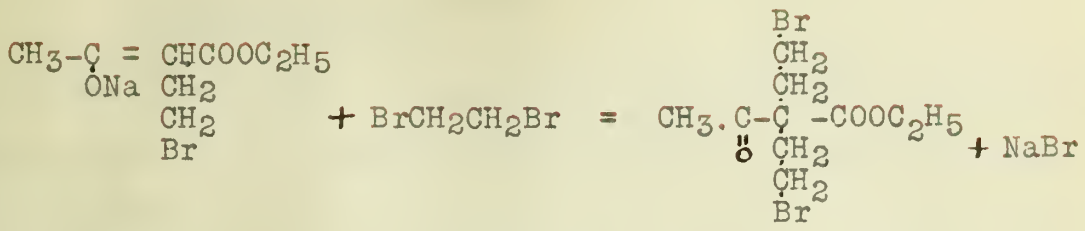
The first was that used by W.H.Perkin[17]. In brief this method consists in first condensing one mole of ethylene bromide with two moles of acetoacetic ester, producing ethyl-$\alpha\alpha$-diacetyl adipate. The desired reaction is,



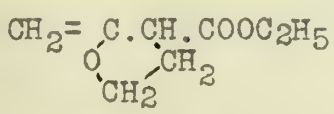


But this is not the only reaction. Perkin states that this product and ethyl-acetyl-tri-methlenecarboxylate are the main products. This second substance would be formed by the enolic hydrogen of β-brom-ethyl-acetoacetic ester being displaced by sodium and then by internal condensation thus,

It hardly seems probable that the possibilities of the reaction would thus be exhausted, for a second molecule of ethylene bromide could condense with the sodium salt of β-brom-ethyl-acetoacetic ester producing $\beta\beta$-dibrom-ethyl-acetoacetic ester as shown by the reaction,



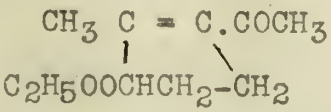
This then could condense with one or two molecules of the ester giving products which might undergo condensations, thus, producing a large number of compounds, though of course those of increasing molecular weight would be formed in relatively smaller quantities. There is some evidence of tri-hydromethylene furfuran carboxylic ester[21],



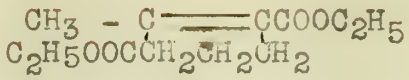
being formed also.

In the present investigation a ten percent yield of dehydracetic acid was isolated in a condensation of one molecule of acetoacetic ester with one molecule of ethylene bromide but it is quite probable that this may have resulted from the process of purification used in this case. This will be treated in detail later.

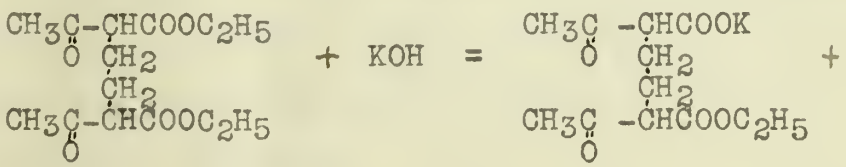
Returning now to the synthesis, Perkin found that ethyl $\alpha\alpha$, diacetyl adipate could not be purified by distillation, even under greatly reduced pressure, as it decomposed for the most part into, ethyl-methyl-dehydropentene-methyl-ketone-carboxylate,



and ethyl-methyl-dehydropentene-dicarboxylate,

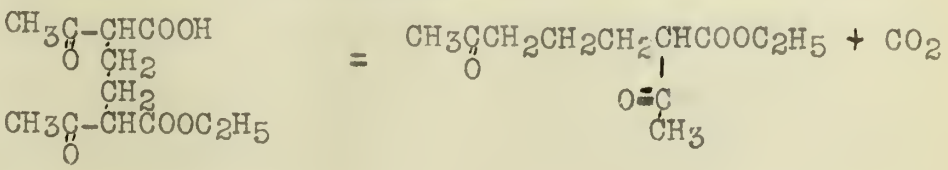


He found, however, that ethyl-acetyl-tri-methylene carboxylate, the unchanged ethylene bromide and acetoacetic ester, at least, could be removed by steam distillation. An ether solution of the residue, which should be mainly ethyl $\alpha\alpha$, diacetyl adipate, was shaken repeatedly with small quantities of a dilute aqueous solution of KOH, immediately run into an excess of dilute acid and extracted with ether. The strength of the alkali was not stated, so (1-10) was used in this work. This, according to Perkin, saponified one ester group producing, by subsequent acidification, ethyl hydrogen $\alpha\alpha$, diacetyl adipate thus,



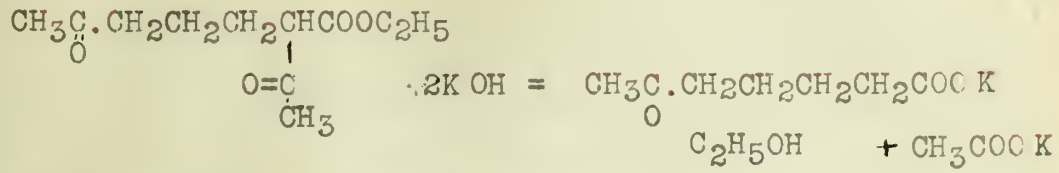
This was found to be an uncertain step in the present investigation. Due to the lack of detail it was difficult to know whether or not the method of the original investigator was duplicated.

Ethyl hydrogen diacetyl adipate should lose CO_2 on heating producing $\alpha\delta$ diacetyl valerianic ester,

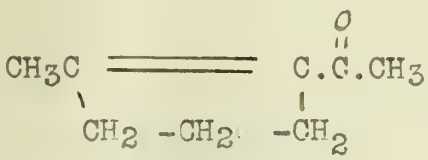


This last substance should undergo the acid decomposition on boiling with a concentrated KOH solution and result in the

formation of δ-acetyl valerianic acid, the desired product.



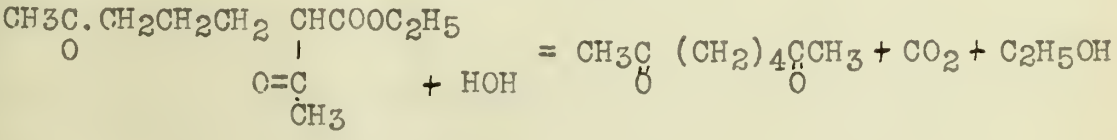
But this, as should be expected, is not a clear cut decomposition and Perkin reports the isolation of methyl-dehydropentene-methyl ketone,

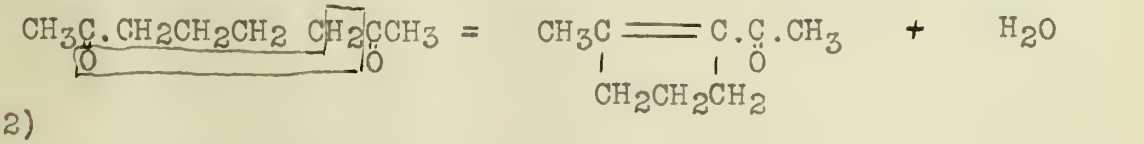


also.

The formation of this can be explained by assuming that αδ diacetyl valerianic acid undergoes the ketone decomposition simulatneously giving diacetyl butane, which, due to the heat of the reaction, loses a molecule of water,

(1)





(2)

Although this method was followed as closely as it was possible from the details given, chemicals were purified carefully and extreme precaution taken to exclude all sources of error; the mass relations, conditions, and methods were altered in detail, the quantity of δ-acetyl valerianic acid was never appreciable or obtained in a degree of purity to be of any use in this investigation. One point might be of interest here.

When the attempt was made to precipitate the silver salt, a beautiful, white, crystalline precipitate was obtained for an instant, then it quickly darkened and became a black amorphous looking mass. The decomposition was probably started by the presence of impurities. Negative results may have been due in a measure to using smaller quantities than did Perkins, he indicated having very large quantities of ethyl $\alpha\alpha'$ diacetyl adipate due to the accumulation from other syntheses. Even theoretically, the method is not at all satisfactory. The most obvious difficulties are, the numerous products of the reaction, the problem of purification, and the one that applies so generally to the reactions of organic chemistry, the very meagre knowledge of the speed of the various reactions and the method of directing them.

Method 11.

The outline of this method was, to prepare 1,4, diacetyl butane by the electro synthesis of the potassium salt of levulinic acid and then to obtain δ-acetyl valerianic acid by the oxidation of one acetyl group.

Synthesis of 1,4, diacetyl butane.

Levulinic acid was prepared from sugar and hydrochloric acid. Large quantities of this were prepared and very good yields obtained. As an example, from 500 grams of sugar, 81 grams of levulinic acid were obtained..

Diacetyl butane was made follwoing the general directions used by Hofer,[25] for the preparation of the same substance.

The apparatus used was the one designed by him[24]. As nearly as possible a current of 2 amperes and a potential of 20 volts was maintained. As to be expected, however, at first the current would be less than this value and the voltage would be higher while towards the completion of the synthesis the current would drop to about an ampereand the potential between the electrodes would become much higher.

The following table is a fair representation of the average condition that prevailed during the process. In some cases the current at the end was less and there were other slight modifications. In this case fourteen storage cells were used.

Table 11.

Time	Current	Voltage.	Observations at Anode.
10.50	1.5	24	Pungent odor, action vigorous
11:00	2.0	25	
11:15	2.0	22	
11:30	2.0	21.5	Few oily drops appeared.
12:oc	2.0	22	A little K_2CO_3 solution added.
1:00	2.0	22.5	A little more K_2CO_2 solution added. Amount of oil increases.
2:00	2.0	21	
2:45	2.0	20	About 1cc of K_2CO_3 solution added.
4:30	2.0	21	Meniscus of oil about 1/3 inch. 1-2cc K_2CO_3 solution added.
7:00	2.0	23	1-2cc K_2CO_3 added.

Table 11.(con't)

Time	Current	Voltage.	Observation at Anode.
8:00	0.9	25.5	Tests acid.This represents the tendency of current and voltage when acid,added K_2CO_3.
8:10	1.9	24.5	
9:10	1.4	26	Action slow.

A solution of potassium levulinate in water (1.5-1) made by neutralizing the acid with the calculated quantity of aqueous KOH was placed in the anode chamber.In the cathode portion was placed an equal volume of a saturated solution of K_2CO_3. Through this chamber a stream of CO_2 gas was continously bubbledin order to prevent the resulting alkali from attacking the porous diaphragm and to the anode chamber it was necessary to add small amounts of a concentrated solution of K_2CO_3,from time to time,to neutralize the acid formed by the electrolysis. It was found necessary to immerse the apparatus in a bath of running water.If this was not done the heat of the reaction caused some of the substance to distill off and would probably result in undesired reactions also.The odor of this distillate was peculiarly pungent.

For maintaining the proper current conditions a rheostat was placed in the circuit and the electrodes were arranged on platinum wires so that they could be adjusted in the solution.

As the process progressed the anode solution darkened and a brownish oil containing the diacetyl butane floated on top.

Quantities of 40 grams of levulinic acid, 18.8 grams of KOH, and 28.8 grams of water were usually used. The process was not generally continued longer than 10-12 hours. At the end, the oily layer was separated, the solution extracted with ether and both combined. The ether extract was very considerable.

The diacetyl butane was purified by dissolving in a solution of $NaHSO_3$. This was best carried out as shown by the following example. To 27 grams of the crude product was added 100 cc of concentrated $NaHSO_3$ solution and 200 cc of water. There was a resinous substance which did not dissolve. This was extracted three times with small amounts of ether. After drying this extract with anhydrous Na_2SO_4 and evaporating off the ether, an oily residue weighing 2.5 grams was obtained. To the aqueous solution 100 cc of concentrated K_2CO_3 solution was added, producing a red coloration. An oil began to deposit on the surface of the solution. This was quickly extracted four times with 25-50 cc portions of ether. Upon drying and evaporating the ether a yellow oily residue weighing 16 grams was obtained. As this was from 40 grams of levulinic acid, assuming it to be pure diacetyl butane, it represents a 66 % yield. It is quite possible that this has other keto substances mixed with it. Hofer does not report better than a 50 % yield. This was one of the best yields obtained in this work. In some cases the oil was changed to a slightly yellow crystalline product on standing in the dessicator. The melting point was found to be 41-42°C (uncorrected). Hofer reports the melting point at 43-44°C.[23]

It might be mentioned here that all of this work was not

carried out with the original Hofer apparatus as it became badly impaired. In fact the best yield that was obtained was from a clumsy affair, made on the spur of the moment, from stove bolts blocks of wood, ordinary porous plate, two Bruehl receivers for cells, and pieces of platinum foil for electrodes. As nearly as possible it was a crude imitation of the Hofer apparatus. One point of difference was in the much smaller amout of liquid that came in contact with the diaphragm, making the resistance somewhat higher.

Oxidation of Diacetyl Butane.

The oxidation of this substance was not so successful. The aim was the differential oxidation of only one acetyl group as completely as possible using a 15 % solution of NaOBr. This solution was added slowly, drop by drop, to the ketone. The subsequent attempt to purify and analyze the product by titration and by the lead salt indicated a substance with a molecular weight that approximated that of δ-acetyl valerianic acid. The method was abandoned for the time.

Method 111.

This method included Gabriel's familiar phthalimide condensation with ethylene bromide, producing brom-ethyl-phthalimide, which in turncould condense with one mole of malonic ester resulting in the formation of β-phthalimide-ethyl-malonic ester[26]. This last product on heating with hydrochloric acid decomposes giving amino butyric acid which upon treating with

nitrous acid and HBr successively, should be converted into γ-brombutyric acid. Finally the condensation of this with acetoacetic ester and subsequent hydrolysis should produce δ-acetyl valerianic acid. The disadvantages of this method are obvious. There was not attempt to carry it to completion.

A point concerning the formation of potassium phthalimide might prove to be useful. It was found that about 10-12 grams of phthalimide dissolved in a liter of 95 % alcohol precipitating a 50 % yield of the salt. While in absolute alcohol a little less dissolved, a 96 % yield of the product is obtained. S. Landsberg[27] in his preparation of the salt does not give the details of the method.

Method. IV.

Following the method of Lipp[28] for the preparation of acetyl propyl alcohol, one mole of ethylene bromide was treated with one mole of the sodium salt of acetoacetic ester. After obtaining β-brom-ethyl-acetoacetic ester in a pure state as possible, it was the aim to condense it with one mole of malonic ester and then by hydrolysis to obtain δ-acetyl valerianic acid. Although this method did not lead to this final result it led to an interesting as well as a perplexing experience for some time.

In the attempt to purify brom-ethyl acetoacetic ester after distilling off the alcohol by gentle suction and heating on the steam bath, the residue was subjected to distillation at ordinary pressure, but the temperature was not allowed to rise

above 173°C. This residue in the distilling bulb, which was acid to litmus, was shaken with a small amount of dilute KOH solution extracted with ether, acidified, and extracted again with ether. This extract left upon evaporation a few crystals surrounded by an oil. Another portion, after extracting with (1-10) Na_2CO_3 solution was treated in the same manner. Upon acidification this time white flaky crystals were precipitated. These were filtered off and their properties determined to be as follows; Melting point 110°C, slightly soluble in cold water and alcohol, but soluble in these solvents hot, slowly soluble in ether, acid to litmus. Gives the iodoform test with NaOBr, proving the presence of an acetyl group, and does not contain bromine. It was difficult to obtain check results for molecular weight by titrating with standard NaOH but this may have been due to hydrolysis caused by using a warm solution. It indicated about 18C. In the first attempt to prepare the lead salt, lead acetate produced a copious precipitate of the free acid from an aqueous solution. It was finally made by boiling with an excess of lead carbonate, but it was difficult to obtain check results, probably due to hydrolysis, though one fraction gave in duplicate analysis 38.75 and 38.90 % of lead. After refluxing for two and one half hours with (1-10) H_2SO_4 the original substance was completely recovered. However, it decomposed rapidly on refluxing with (1-10) NaOH. Suspecting it to be dehydracetic acid, a little was warmed with aniline and thencautiously acidified with (1-10) HCl. After a short time a flaky, white, precipitate slowly formed and floated in the liquid. This was filtered off and its

melting point found to be 118°C, corresponding to that for dehydracetanilide[29]. This proved conclusively that the substance is dehydracetic acid. In one case 75 grams of the original product was extracted with 300 cc (1-10) Na_2CO_3, 75 grams of the acid was obtained. Thus it is seen that ten percent of the products of the condensation had been converted into dehydracetic acid.

A small portion of the residue was refluxed with a solution of sodium alcoholate[30] and analyzed for bromine by the Volhard method. There was not more than 1 % present. This suggests that it may have disappeared in the distillation and may account for the formation of dehydracetic acid. Still more evidence in favor of this is that the acetoacetic ester was found to contain none of the acid, nor could it be isolated from a similar condensation product that had not been distilled afterwards.

Method V.

This method promises to be successful. It consists in the formation of γacetyl propyl alcohol fromacetoacetic ester, ethylene bromide and subsequent hydrolysis. The conversion of this to the bromide, its condensation with malonic ester and the hydrolysis of this product completes the process.

The details of this synthesis will be given more completely. For the preparation of the alcohol and bromide the method of Lipp[31] was followed.

First Attempt.

γ-acetyl propyl alcohol.

24 grams of metallic sodium were added gradually to a flask containing 260 grams of absolute alcohol, connected with a reflux condenser, the open end being protected by a $CaCl_2$ tube. Keeping the contents of the flask cool, 130 grams of acetoacetic ester were added and then 196 grams of ethylene bromide. This mixture was heated on the water bath for eight hours with a reflux condenser connected with a calcium chloride tube. At the end of four hours the solution was filtered from the NaBr and found still to be alkaline. At the end of eight hours the solution was neutral to litmus. The next day the alcohol was distilled off from the steam bath, the last portion being removed by reducing the pressure to 260mm. The residue weight 160 grams, was shaken with 100cc of (1-10) NaOH solution. Lipp did this to remove any unchanged acetoacetic ester. According to Perkin's results, one would expect this to saponify one of the ester groups of the αα, diacetyl adipate which would be present also. The question, why this might not remove some of the β-brom-ethyl-acetoacetic ester also suggests itself. The amount or strength of the solution which he used, however, was not stated. At any rate the residue lost 35 grams of something. This extract has not been investigated as yet. The product remaining, weight 125 grams, was mixed with 200 cc of water and refluxed over a gauze for five hours. After standing over night 80 grams of a yellow oily layer was separated from the solution. According to Lipp this is ethylene bromide and ethyl αα, diacetyl adipate, though undoubtedly

it contained another products as well. A very good example of salting out was obtained by saturating the aqueous solution with K_2CO_3. 58 grams of a yellow oil with suspended material separated. Upon filtering this, considerable solid alkali was obtained. The filtrate separated into two layers one of which was found to be water, the other, which was slightly brown, contained the alcohol with impurities. The product was shaken with (5-6) times its volume of ether. The substance did not entirely dissolve and left a cloudy solution which cleared upon adding a large amount of anhydrous sodium sulphate. After two hours the clear solution was filtered from the sodium sulphate and the ether was distilled off. Weight of residue was 17 grams. Has a peculiar odor. This was fractionally distilled the results being shown by the table.

Table

Fraction	Pressure	Temp.	Wt.
1	20 mm	95	2 gms.
11	20 mm	95-102	1.8 "
111	20 mm	102-105	5.0 "
1V	20 mm	105-110	few drops.

All fractions except the first which smells ester like have a nutty odor and are all colorless. There was vigorous boiling before distillation was observed but no condensation. This fact and the final weight, showing that some low boiling substance, probably ethyl alcohol, has been lost.

A drop of fraction 111 gave a little precipitate with a saturated solution of $NaHSO_3$. Does not give a coloration with

alcoholic $FeCl_3$. This fraction was taken for γ-acetyl propyl alcohol and represents a 5 % yield. Lipp reports a 20 % yield but the purity of his substance is questioned.

Preparation of γ-Acetyl Propyl Bromide.

Fifteen cc of HBr, specific gravity 1.78, in a small flask was cooled to - 5°C by a freezing mixture. Keeping it at this temperature 5 grams of acetyl propyl alcohol was added, drop by drop, during a period of about half an hour. The mixture very slowly colored and finally became brownish red with a distinct raspberry odor. After remaining in the freezing mixture for about fifteen minutes the solution was slowly added to 5-6 times its volume of distilled water in a flask surrounded by the freezing mixture. Almost immediately there was a separation of a colorless oily substance. The solution was extracted with ether three times, saturated with NaCl, and extracted three times again. After standing over Na_2SO_4 for an hour, the ether was evaporated by suction, leaving 5.5 grams of a light yellow liquid. On standing a few hours it darkened slightly.

The product was purified by vacuum distillation. For this purpose a short water condenser was used and the receiver was immersed in ice water. At a pressure of 21 mm and a temperature of 87-89°C, 3.5 grams of a clear colorless liquid was obtained. The odor of raspberries was practically gone. The rest of the product remained in the distilling bulb as a black resinous mass. The distillate turned slightly dark on standing over night. The yield of γ-acetyl propyl bromide is 44 % theoretical.

Condensation of γ-Acetyl Propyl Bromide with Malonic Ester.

0.48 gram of metallic sodium was dissolved in 5 grams of absolute alcohol. 3.4 grams of malonic ester was gradually added and then 3.5 grams of γ-acetyl propyl bromide. The flask was connected with a reflux condenser, protected by a calcium chloride tube. Reaction began without warming but not vigorously. Warmed on the steam bath one half hour. Filtered off the NaBr, evaporated the alcohol from the steam bath by gentle suction, cooled, dissolved in ether, dried the solution with anhydrous sodium sulphate and after evaporation of the ether 1.8 gram of a light brown liquid, with an ester odor, was obtained. The yield was too small in this case to attempt purification.

Saponification of γ-Acetyl Propyl Malonic Ester.

The product of this last condensation was mixed with 10 cc of 50% H_2SO_4 and warmed very cautiously. The solution rapidly darkened and considerable resinous material was formed. The substance seemed to be completely decomposed by this treatment, as the attempt to isolate the product failed. This was probably due to the polymerization of the keto group.

Second Attempt.

This attempt was practically a repetition of the first except in two points. After the first condensation, the substance was not shaken with KOH solution but this did not improve the yield of the alcohol. The hydrolysis of the second condensation

was not repeated with a 50 % solution of H_2SO_4 but with a 4 % solution of HCl. Carbon dioxide was found to be slowly evolved. After refluxing four hours the solution was cooled, made alkaline with saturated K_2CO_3 solution, extracted three times with ether, acidified, and then extracted six times with ether again. After the drying and the evaporation of the ether, a small amount of liquid with the odor of the lower aliphatic acids was left. After remaining over night in a vacuum dessicator, containing soda lime, the substance was found to be crystallized. On attempting to take the melting point, it sintered all the way from 40-100°C and then melted from 100-115°C, thus indicating a mixture. It is probable that this may contain γ-acetyl-propyl-malonic acid and δ-acetyl valerianic acid. Lack of time required the investigation to be discontinued at this point for the present.

I wish to thank Dr. C. G. Derick for his constant personal attention and interest and for his indulging and optimistic spirit shown throughout this investigation.

C R Wilson

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